Agenda

• General Overview – Why are we here?  Bob Steininger [10 min]

• User Perspective: What’s the pain and what would help users?
  – Acceleron – B Steininger – small company perspective [15 min]
  – Amgen – D Low – large company perspective [15 min]
  – GSK – A Pralong – vaccines and other industry perspective [15 min]

• Supplier perspective: What’s the pain and what would help suppliers?
  – GE – J Carter [10 min]
  – Sartorius – L Okhio [10 min]

• Regulatory perspective: What’s the pain and what would help regulators?
  – Speaker TBD [15 min]
Agenda (continued)

- ASTM SUT Working Group Activity – J Bray
  - General background – [15 min]
  - Extractables – J Bray to present J Vogel info [5 min]
  - Timing – Bray [5 min]

- Other organizations working on SUT standards–
  - BPOG activity Tony White [10 min]
  - PDA group white paper – Bob Repetto [10 min]
  - BPSA activity on Quality System Matrix – J Carter [5 min]

- Open discussion

- Review action – Steininger [10 min]
Overview
Why are we here?

Bob Steininger
User Perspective

Acceleron – Bob Steininger
Amgen – Duncan Low
GSK – Alain Pralong
Enabling Early Develop with Single Use Technology

The Advantages and Challenges of Operating a GMP Facility Based on Single-Use Equipment

Bob Steininger
SVP, Manufacturing
10 April 2013
Acceleron Pharma Company Overview

• Founded in 2003 in Cambridge, MA
• Privately held
• Partnership with Celgene for anemia-targeting programs and Alkermes for novel second generation proteins
• Currently ~75 individuals
• Fully integrated biotherapeutic R&D infrastructure
  – Protein engineering
  – In vivo pharmacology
• GMP protein manufacturing facility with six fusion proteins in development and four in the clinic in 2013
• Focus on novel GDF related proteins that modulate the growth of bone, muscle, fat and the vasculature
Company Pilot and GMP Manufacturing Strategy

• Bring Research Reagent, Pilot and GMP production in-house to control quality, capital outlay, and timelines for early phase products
  
  – Make initial research material to explore biology (rodent, dog, human, etc.)
  
  – Use same technology to make non-GMP material for early toxicology studies
  
  – Using same, platform process, quickly make and release phase 1 and 2 material for clinical trials minimizing capital expenditure
GMP Facility Design Details

• Approximately 12,000 ft$^2$ of GMP Area, with ~4500 ft$^2$ of production area

• Separate air handling systems for each of the four processing areas. Separate entry area to each process area off common clean corridor

• SOPs in-place to allow different products in the four manufacturing areas

• All media and buffers delivered from adjacent warehouse as portable liquid or pumped from controlled corridor through wall to controlled area.
ACCELERON PHARMA
128 SIDNEY STREET
N.T.S.

Acceleron 128 Sidney CMF Production Area
Process Equipment Design Criteria

- Single Use Process Equipment for all Operations – except columns and DO probes (resins dedicated to product) – **No Sterilization or cleaning validation**
- All process equipment without CIP (except columns)
- All buffers, product intermediates, and waste contained in bags within Totes
- Buffers and media delivered steriley in limited to 20L to 500L aliquots – **No WFI, DI Water Systems**
- All liquids transferred using disposable tubing
- All disposables delivered steriley
- Sterile connections made using tube welding and CleanPak connections
Vendor Audit/Qualification Program Essential

What we look for from our vendors!

- **Vendor Qualification Classification**
  - Accepted/Approvable Certified Vendor
  - Utility Validation Program

- **Vendor Ranking Criteria**
  - Critical Part; Sole supplier; Lead Time;
  - Cost, Quality; Vendor-History

- **Quality Agreement**
  - Change Control/Deviation Notification
  - Confidentiality Disclosure

- **Audit Program**
  - GMP Mfg, Cleanrooms, Quality Systems, Utilities
  - Med. Device QSR vs. GMP
Rely on SUT Vendor for the Following:

• Initial Extraction\Leachable evaluation

• Documentation of design and design changes

• Effect of Gamma Irradiation on components and sterilization validation (based on background level of bacteria)

• Consistent assembly process to assure a high probability of maintaining integrity
Additional Challenges

• Vendor Quality Programs – Mistakes are more difficult to catch externally
• Cost of small orders and limited influence
• Consistent Availability of Raw Materials
• Shipping of Material: $0.1-0.8 /1000 Liters/mile
• EU Testing and Release of Sterile Solutions in Bags
• Consistent testing for release and stability
User Perspective: Amgen

Duncan Low
Evolution and impact of single-use technology

Alain Pralong
VP New Product Introduction & Technical Life Cycle
April 10th 2013, London, UK
Content

- Overview on biopharmaceutical industry
- Paradigm shift
- Evolution of single-use technology
- Holistic approach and integration
- Summary & Conclusion
Constraints of biopharmaceutical industry

- Traditional technologies – chemical engineering
- Very expensive – CAPEX
- Labor intensive – 4 to 5 years
- High OPEX – utilities, personnel, raw materials
Wishes of biopharmaceutical industry

- Minimal CAPEX investment
- Minimal time for build and commissioning
- Significant COGS reduction
- Sustainability and efficient resource use
La perfection est atteinte,
non pas lorsqu'il n'y a plus rien à ajouter,
mais lorsqu'il n'y a plus rien à retirer.

Antoine de Saint-Exupéry
Evolution of single-use technologies

- Massive development of single-use tools
- Broadening of applications
- Multiple suppliers – market consolidation
- Major progress in regulatory acceptance

Shire says new plant will add to Replagal, Vpriv capacity
Published on 17/01/11 at 09:52am on www.inpharm.com

UK drugmaker Shire has completed construction of a new manufacturing facility for its orphan disease drugs Replagal and Vpriv, and expects it to come online later this year.

The new large-scale facility in Massachusetts, USA, is expected to seek approval to make Fabry disease treatment Replagal (agalsidase alfa) later this year and Vpriv (velaglucerase alfa) for Gaucher disease in 2012, according to a *Bloomberg* report.

The 200,000 sq.ft. facility in Lexington has cost upwards of $250 million to set up and is claimed to be the largest bioprocessing facility in the world using disposable manufacturing equipment. In addition to cell culture production areas, the plant has a clinical suite and warehousing units.
First steps

- Replacement of glassware
- Maximal reduction of preparation time
- Maximal reduction of contamination risks
- Massive ergonomic improvement
Development

Medium and buffer preparation
Development

Operation and sampling of bioreactors
Maturation

Product contact only by single-use components
Maturation

Bioreactor setup

A B C D E F
Maturation

AIEX chromatography
Maturation

Manufacturing platform for clinic and market
Maturation

- CEMs provide grade C environment
- CEMs provide segregation
- DSP process is fully closed
- Only sterile de- / connection technology
- Product always fully protected from operator

Higher quality standard achieved than with traditional technology!
Maturation
Maturation

- Fully disposable process @ 200-L scale
- Built and operated within 8 months
- Reasonable costs – 6 million US$
- Simple – reduced to the minimum
- Results with MAbs and Adenoviruses
Conclusion on single-use technology

- Single-use technology available for viruses and MAbs
- Massive development in the last 10 years
- Significant acceleration and cost reduction
- Fulfills GMP requirements
- Development of single-use DSP technologies ongoing

- 3-dimensional binding capacity
- Up to 25x higher throughput
- Single-use while still being multi-use
Facility of the future

- Modular facility within a shell
Facility of the future
Facility of the future
Facility of the future
Facility of the future
Vaccine development = multi-step process

from idea

to product
Operational Excellence

- Multiple activities need to converge to a fully integrated concept
  - Process / clinical development
  - QA / QC / RA
  - Manufacturing
  - Procurement
  - Supply chain

Operational Excellence
Quality through holistic approach

- End-to-end product development plan
- Involving all contributors
Quality through holistic approach

- Structured through stage gates

Diagram showing stages:
- G1: Commit to Research
- G2: Commit to Candidate Development
- G3: Commit to Phase I/II
- G4: Go to Final Scale
- G5: Commit to Phase III
- G6: Commit to File & launch
Quality through holistic approach

- Product Development Value Stream
  - Process design – Kaizen / Genchi Genbutsu
  - Flow of material & information - Kanban
  - Coordination with stake holders - Nemawashi
Summary

- Massive evolution of single-use technologies
- Heavy impact on facility design and operation
- Need for significantly higher level of operational excellence
- Boost in ergonomics and training needed

1982 1994 2009
Conclusion

- Need for standards and guidance:
  - Leachables & extractables
  - Risk assessment and mitigation
  - Dual sourcing
  - Closure integrity
  - Validation
Supplier Perspective

GE Healthcare – Jeff Carter
Sartorius Stedim – Laura Okhio
Pain points for single use equipment suppliers

Standardization candidates

Jeffrey Carter PhD
GE Healthcare Life Sciences
Quality data expectations

How much of what kind of data are expected?
In what format are they most useful?
What is reasonable to provide during audit versus as hard copy?
What are the expectations with respect to repeating experiments from time to time?
Particulates

USP <1>: “essentially free”
EP: “practically free”

Application of pharmaceutical standards to equipment: particles/dose → particles/m²

Chemical make-up of particles...

What does FDA think of the Stimuli proposal? At this point in time, they’re not in support, Shabushing admitted. “They’re concerned about setting any kind of limits, and want firms to establish their own limits on a case-by-case basis... If they set the bar, there will not be a continuous effort to reduce the amount of particulates in products.” He added, “We need to work with USP to further engage FDA on this topic.”

Leak Testing

*de facto* standards for filters are being applied to SU equipment.

Limits to detection are high due to pressure limits.

Elaborate methods are being developed and protected.

Are they needed? What is appropriate?
Biocompatibility

USP <87> <88>
ISO 10993-3, 4, 5, 6, 10, 11
Both?

Application of medical device standards to SU manufacturing equipment has been the norm for decades.
Connectors

VHS and Betamax
Multiple connector formats
Requests for consolidation to one format
Requests for innovation
“Legislate” the format or allow the market to decide?
Does IP lead to sole ownership of the chosen format?
Sartorius -Stedim

Laura Okhio-Seaman, Director, Validation Services, North America
Single-use manufacturing from the design phase

Biopharmaceutical upstream and downstream processes have a practical and economic benefit in implementing single use manufacturing.

Companies who consider single use technologies from the early design stage of a new facility or retrofit can optimize the facility layout and simplify the process thus enjoying the following widely recognized advantages:

- Superior process performance
- Time to market reduction
- Ease of use
- Flexible facilities
- Cost reduction
We get it:

Our customers do not need to simply get a SUS validated. What they need is:

- Process and product safety
- Economic safety
- A high degree of cGMP compliance
- Reliable information sources
<table>
<thead>
<tr>
<th>Qualification tests</th>
<th>Monitoring tests</th>
<th>Lot release tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIOCOMPATIBILITY TESTING</strong></td>
<td>• Bacterial Endotoxins test USP&lt;85&gt; and E.P. 2.6.14</td>
<td>• 100% visual testing of bag and seal</td>
</tr>
<tr>
<td>• USP&lt;87&gt;: Biological reactivity tests, In Vitro</td>
<td>• USP&lt;788&gt; and E.P. 2.9.19 : Particulate</td>
<td>• 100% air pressure leak test</td>
</tr>
<tr>
<td>• USP&lt;88&gt;: Biological reactivity tests, In Vivo</td>
<td>• ISO 11737: Bioburden</td>
<td>• Technical drawing compliance</td>
</tr>
<tr>
<td><strong>MECHANICAL PROPERTIES</strong></td>
<td>• ISO 11137: Sterilization of Medical Devices</td>
<td>• Dimensional check</td>
</tr>
<tr>
<td>• Tensile strength</td>
<td>• ISO 14644: Cleanrooms environmental controls</td>
<td>• Packaging and labelling inspection</td>
</tr>
<tr>
<td>• Elongation at break</td>
<td></td>
<td>• Gamma sterilization</td>
</tr>
<tr>
<td>• Seal strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Air leak test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extractables and Leachables- Validation guides</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GAS TRANSMISSION PROPERTY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ASTM D3985: Oxygen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ASTM F1249: Water Vapor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>USP&lt;661&gt; TESTS FOR PLASTICS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.P. 3.1.7.: EVA for containers and tubing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.P. 5.2.8. on TSE-BSE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Product Qualification and Quality Control meet the requirement of aseptic processing
Each Single Use System is defined by Materials Of Construction (MOC).

Extractables and leachables testing is conducted and results compiled into comprehensive guides.

Subsequent introduction of the same MOC in a new SUS is streamlined thus avoiding repeating the original tests.

Once a material with the needed properties is identified more SUSs can be developed utilizing that material.

More cost savings are realized.
OUR HEADACHE:

• Many common raw materials can be sourced from multiple raw materials suppliers. The suppliers of raw materials should cooperate in supplying information to an exhaustive degree of MOC. The information should be available to both user of the SUS manufactured from the MOC, and to the end user.

• This degree of disclosure may not be readily achieved. Establishing non-disclosure agreements may be required.

• No Standard guidelines for E and L testing from the FDA. Extensive Validation packages available, yet it is not enough!

• End-users requiring “customization” of products which can cost time and money

• End users putting so much detail into SOP’s that we are often forced to stockpile components, if for example, there is a resin change

• End-users often require what is deemed IP by the supplier

• End-users have concerns about security of supply... so do we

• As a supplier we have put a risk management strategy in place, secondary sourcing

• Scale up capability...... as one size does not fit all

• End-user feedback is often slow in coming, but is urgent once it comes.... collaboration should be upfront
Thank You!
Regulatory Perspective

No representative available for this meeting
ASTM SUT Working Group Activity

Overview - Jim Bray
Extractables Standard – Jim Vogel
Change Control Standard – Sally Kline
Evolution of Activity

- 9-month iterative process got us to today’s presentation
  - Original discussions started summer 2012 – BPSA group focused
  - Work originally started focused on updating existing ASTM extractables standard

- Bob Steininger brought focus October 2012
  - Working group previously discussed formed and expanded
  - Monthly conference calls with actions and follow up

- As we added members for this effort, the backgrounds caused our focus to expand significantly to include a much wider range of topics within the SUT area

- 10 organizations represented
  - End Users 4 Acceleron Pharma, Amgen, Genentech, GSK Biologics
  - Suppliers 3 GE Healthcare, Sartorius Stedim, ThermoFisher BioProcessing
  - Testing Lab 1 Validation Resources
  - General Interest 2 2 consultants (bioprocessing backgrounds)
  - Regulatory 0 Bob Steininger still working to get representation

- Membership includes wide participation on industry groups working on guidance documents – BPSA, PDA, BPOG, ISPE
## Focus Topics

Generated a list of potential topics with a rank order system

<table>
<thead>
<tr>
<th>Standard Topic</th>
<th>Points</th>
<th>Degree of Difficulty</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extractables / Leachables</td>
<td></td>
<td></td>
<td>Work in progress. Target April / May draft</td>
</tr>
<tr>
<td>Change Control / CMC package</td>
<td>19</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Standardization of products / components</td>
<td>17</td>
<td>10</td>
<td>Requires various manufacturers to agree on standard; likely simpler for areas such as fittings which are predominantly dimensional; much harder for bags where you are dealing with chemistry and proprietary formulations. BioPharm end users will likely take leadership role in forcing standardization.</td>
</tr>
<tr>
<td>Particulates</td>
<td>16</td>
<td>4</td>
<td>USP 788. Significant work already done with microelectronics and medical devices which can be used to develop consensus standards</td>
</tr>
<tr>
<td>Quality Template</td>
<td>12</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Physico-chemical characterization: e.g. Tg, DMA Scan, Use Limits</td>
<td>9</td>
<td></td>
<td>BPSA activity to update Quality Test Matrices should aid this.</td>
</tr>
<tr>
<td>System Integrity</td>
<td>8</td>
<td>5</td>
<td>Lot of technology on integrity for individual components; more challenging when dealing with assembly of large number of components.</td>
</tr>
<tr>
<td>Shelf Life / Transportation</td>
<td>0</td>
<td></td>
<td>Currently part of ISO 111137</td>
</tr>
</tbody>
</table>
Other Relevant Groups

General: PDA Task force on Single Use Equipment; ISPE

<table>
<thead>
<tr>
<th>Standard Topic</th>
<th>Existing Standards / Guidance Documents</th>
<th>Other Organizations Currently Working in Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extractables / Leachables</td>
<td>ASTM E2097-00 (2006) – requires revision</td>
<td>BPSA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BPOG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PQRI (AAMI)</td>
</tr>
<tr>
<td>Change Control / CMC package</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standardization of products / components</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Particulates</td>
<td>ISPE Good Practice Guide</td>
<td>PDA: SUT technical report pending</td>
</tr>
<tr>
<td></td>
<td>USP</td>
<td>BPSA (AAMI)</td>
</tr>
<tr>
<td>Quality Template</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physico-chemical characterization: e.g. Tg, DMA Scan, Use Limits</td>
<td>BPSC: “Component Quality Test Matrices” 2007. Update is in progress.</td>
<td></td>
</tr>
<tr>
<td>System Integrity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shelf Life / Transportation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ASTM E2097
April 2013 Update
James Dean Vogel
The Bioprocess Institute
Team

- Alain Pralong
- Ekta Mahajan
- Jeff Carter
- Sally Kline
- Sarah Robinson
- Christopher J Smalley
- James D. Vogel
Summary

• We discussed getting started on the changes to E2097.
• The general consensus was to wait for the BPOG group’s recommendations.
• We briefly reviewed the ASME BPE and its proposed extractables changes.
• Some specific points were discussed and listed below:

1. Scope

1.1 This guide covers procedures and test methods for process component qualification by the end user. The goal is to assess the safety impact of extractables from non-metallic process components used in contact with bioprocessing solutions. This encompasses the impact of extractables on the safety of the final product as it passes through the various stages of the manufacturing process. This guide is not designed for evaluation of metallic materials, final product container/closures or those components intentionally added to the product or production streams during the manufacturing process. Testing of solids and extracts is specified in other ASTM standards. Materials must be qualified by specific use.

1.2 The values stated in SI units are to be regarded as the standard.

1.3 There is no companion guide available.

1.4 Safety/Fire Hazards: Extractions with organic solvents will be infrequent under this guide, but, when used must be treated as potential fire/explosion hazards.

1.5 This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.

2. Referenced Documents

2.1 ASTM Standards:

D4951 Test Method for Determination of Additive Elements in Lubricating Oils by Inductively Coupled Plasma Atomic Emission Spectrometry

F619 Practice for Extraction of Medical Plastics

3. Terminology


3.2 Definitions:

3.2.1 biopharmaceutical—any drug product produced from living organisms.

3.2.2 biotechnology solution—a solution containing or producing products from living microbial, animal or plant cells or by the enzymes from those cells.

3.2.3 biotechnology product—a discrete chemical entity produced by growing single cell organisms with unique genetic information.

3.2.4 elution cytotoxicity—see USP.

3.2.5 emission spectrographic analysis (ESA)—an analytical technique for determining metals in a sample vaporized in a plasma arc.

3.2.6 extractables—residues from solid process components not intentionally part of the product process stream.

3.2.7 fermentation—the biochemical reaction process where microorganisms in a nutrient medium convert a feedstock to a product.

3.2.8 inductively coupled plasma (ICP)—an analytical technique designed to quantitate chemical elements.

3.2.9 materials of construction—high molecular weight or solid materials, used in biopharmaceutical process equipment which contact process solutions and can potentially release extractable residues.

3.2.10 non-volatile residue (NVR)—non-volatile material remaining after evaporating a solvent into which the residue has been extracted (See USP).

3.2.11 oxidizable substances (OS)—chemical compounds which may be oxidized by potassium permanganate under specified conditions (See USP).

3.2.12 product contact material—a material which physically contacts a solution containing the chemical entity designated the product.
Definitions

• Redefine the definitions to provide more clarity to the community and align with other references. Candidates to address are:
  – Extractables
  – Leachables
  – Other
Model Solvents

• Define what model solvents really mean?
• When do we do leachables? Or can we leverage Extractables (including model solvents) instead?
• Align with Pharmaceutical Engineering paper.
Standardization of Single Use Components’ Extractable Studies for Industry
by Ekta Mahajan, Trishna Ray-Chaudhuri, and James Dean Vogel

Introduction
The use and implementation of single-use technologies continues to grow in the biopharmaceutical industry. One of the key components to qualifying and implementing these new technologies is the extractable and leachable profile.

The definitions are referenced, as follows from the Extractables and Leachables Subcommittee of the Bio-Process Systems Alliance.¹

Extractables: chemical compounds that migrate from any product contact material, including elastomers, plastic, glass, stainless steel, or metal component(s) and exposed to an appropriate intake and storage conditions of time and temperature.²

Leachables: chemical compounds that typically are a subset of extractables, that migrate into a drug formulation from any product contact material, including elastomers, plastic, glass, stainless steel, or metal component(s). This is a result of contact under normal process conditions or accelerated storage conditions. These are likely to be found in the final drug product.³

With the development of new single-use technologies, system, and new products, it is becoming more critical to consider the leachable profiles of similar types of components. There have been discussions and recommendations for bracketing the study; however, every company and supplier follows a different protocol.

This article will list typical model solvents that are evaluated by end users, possible extractor conditions, and analytical techniques that should be included in a standard. The identified extractable criteria should be analyzed and compared to standard guidelines such as the International Conference on Harmonization (ICH) Guidelines and European Pharmacopoeia (EP) Monographs.

Recommendation for Model Solvent Approach
End users have received validation packages that are comprehensive but differ significantly in protocol testing for the extractable studies. New suppliers are at times confused on what type of extractable studies should be run for their new single-use systems. Thus, running extractable studies under various conditions and comparing the same sample’s surfaces reveals some reality, storage extraction conditions (temperature, time, and test point), model solvents, and the same analytical techniques are needed.

This will provide guidance to single-use suppliers in performing a consistent extractable study. At the same time, the end-users will be able to compare single-use components from various suppliers and

<table>
<thead>
<tr>
<th>Model Solvent System</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 M HCl 7.1 pH 2.0</td>
<td>Predominantly high pH extreme and removal process conditions.</td>
</tr>
<tr>
<td>50% Ethanol</td>
<td>Predicts extract if the process is optimized and elimination of a component.</td>
</tr>
<tr>
<td>0.1 M HCl, 7.1 pH</td>
<td>Predominantly high pH extreme and removal process conditions.</td>
</tr>
<tr>
<td>0.1 M Sodium Chloride 0.9%</td>
<td>Predicts extract if the process is optimized and elimination of a component.</td>
</tr>
<tr>
<td>0.1 M Sodium Chloride 0.9%</td>
<td>This is a chemical aspect.</td>
</tr>
</tbody>
</table>

Table 1: List of solvents for extractable study.
Standard Methods

• Define/refine standard sample preparation methods?
• Define/refine standard analytical methods?
Risk vs. most severe

- Risk based approach with considerations-Comment to ensure proper risk assessment is employed to do the proper tests vs. rounding up. We discussed how the tendency is to always do the most severe tests and we want to be sure the risk concept is included.
  - Time-Differentiate between long term exposure, e.g. bag vs. transient, short time, e.g. tubing. Does two years make sense?
    Reverse hockey stick plot? Many compounds reach a limit early, and taper off. We discussed the need to reference a study to help prevent rework.
  - Surface area-Bags vs. filters were discussed and their differences and the complexity of components needs to be considered.
  - Do different things come out in different conditions?
Alignment

• Alignment for non-standard content with community…. (ISPE like ASTM E2500?)
• We discussed the model of ASTM E2500 and how ISPE worked with ASTM and an option for information, which is not ready for the standard.
• Suggestions from the E55 meeting?
Projected Timing

• Timing-We discussed that BPOG is close and we will want to have output by the end of 2013.
• Wait for BPOG –Spring/Summer 2013
• Draft changes-Summer Fall 2013
• Submittal by year-end 2013
Actions

• Group to review ASTM E2097 and mark it up for where potential changes should go.
Change Control

Sally Kline – Amgen
Ekta Mahajan – Genentech
Alain Pralong - GSK
Bob Steininger - Acceleron
The role of change controls for suppliers and end users:

- Change controls and their transparent communication are critical to reducing the risk of use of single use components.
- Suppliers must have a robust change control process for their entire supply chain.
- End users and suppliers should have a common definition of the impact of change controls.
- Change controls can range from simple to extensive and expensive to implement.
- Lack of adequate change controls can result in extensive root cause analysis investigations.
Examples of Changes that Plague End Users

- New polymer / resin
- Accessory components in contact with process stream
- Manufacturer that assembles system with non-identical components
- Manufacturer of “equivalent” resin
- Manufacturing process changes
Determining a common definition of change controls for the industry for single use systems:

• Current draft proposal is a risk based approach which rates four key criteria:
  1. Time required to evaluate the change control
  2. Amount of testing/resources required to evaluate change control
  3. Current understanding of the technology or science supporting the change
  4. Impact on the biological process of the change

• The product of the four criteria will determine the risk and difficulty to implement for the end user

• The change controls will be categorized into tiers with recommended testing and communication time prior to implementation
## Standard Development Outlook

<table>
<thead>
<tr>
<th>Standard Topic</th>
<th>Plans</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extractables / Leachables</strong></td>
<td>Work in progress. Target summer draft</td>
</tr>
<tr>
<td><strong>Change Control / CMC package</strong></td>
<td>Activity to define user requirements has started</td>
</tr>
<tr>
<td><strong>Particulates</strong></td>
<td>Pick this activity up once Extractables / Leachables standard is in advanced state of review</td>
</tr>
<tr>
<td><strong>Quality Template</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Physico-chemical characterization: e.g. Tg, DMA Scan, Use Limits</strong></td>
<td>BPSA activity to update Quality Test Matrices should aid this.</td>
</tr>
</tbody>
</table>

Continue to solicit input for other Standards needs & coordinate with relevant organizations.
Other Organizations Working on SUT Standards

BPOG – Tony White
PDA White Paper – Bob Repetto
BPSA Quality System Matrix – Jeff Carter
Determination of a
STANDARD EXTRACTABLES
PROTOCOL
for use by Suppliers of Single Use
Technologies in the Biotech industry
Tony White
Director, BPOG
10 April 2013
Agenda

- BioPhorum Operations Group
  - The Disposables Workstream
  - ISPE outline proposal
  - BPOG value add and next steps
BioPhorum Operations Group (BPOG)

- BPOG is a global collaboration of commercially active biopharmaceutical drug substance companies

- Since 2008 it has grown to
  - 20 member companies
  - Fielding over 500 representatives
  - Connecting, collaborating and accelerating practices in 12 Workstreams

- BPOG
  - Has an agenda set to address common company interests
  - Drives collaboration like a project to achieve agreed deliverables
  - Can quickly gather a group of manufacturers/users on a opportunity
  - Is not a standards body or representative of suppliers, so works with and through other bodies to realise change
Members are sponsored from VP level and engagement is driven by operational goals

- AbbVie
- Amgen
- Bayer
- Baxter
- Biogen
- BMS
- Gallus
- Genentech/Roche
- Genzyme
- GSK
- Janssen
- Lonza
- MedImmune
- Merck & Co., Inc
- Novartis
- Pfizer
- Sanofi
- Regeneron
Agenda

- BioPhorum Operations Group
- The Disposables Workstream
- ISPE outline proposal
- BPOG value add and next steps
In July 2012, twelve BPOG member companies met to share experiences and agree a program of collaboration on drug substance disposables

The immediate focus was agreed to be

- **Standard Extractable Protocol**
  - To refine and endorse the ISPE proposal for a standard extractable protocol for disposables used in the biopharmaceutical drug substance industry
  - To communicate these needs to the supply industry

Following this the group will consider

- **Leachables Guidance**
  - Endorsement of existing guidance to encourage consistency

- **Cell Culture Performance**
  - Agreement and promotion of a model for success

- **Physical Standardisation and/or Lead-time Compression**
  - Encourage the supply industry to accelerate towards this position
Agenda

- BioPhorum Operations Group
- The Disposables Workstream
- ISPE outline proposal
- BPOG value add and next steps
‘Standardization of Single Use Components’ Extractable Studies for Industry’

- Published in Pharmaceutical Engineering, May 2012
- Authored by Ekta Mahajan, Trishna Ray-Chaudhuri and James Dean Vogel
- Work originated by the ISPE CoP on Single Use Systems
- Article proposed
  - A standard protocol for extractable studies which would take away need for additional studies
  - Called for the endorsement of a suitable User and or Supplier grouping
- The protocol has three parts

**Part I**
- **Model Solvents**
  - WFI pH 11-12 (0.5N NaOH)
  - 5M NaCl
  - PBS
  - 50% Ethanol
  - WFI pH (0.1M Phosphoric acid)
  - 20% Polysorbate 20
  - WFI neutral

**Part II**
- **Time points and temps**
  - 0 hours 25°C
  - 48 hours 40°C
  - 30 days 40°C
  - 120 days 40°C

**Part III**
- **Analytical techniques**
  - pH measurements
  - Conductivity
  - TOC
  - Screening of metals
  - Volatile Organic Compounds (VOC) with direct injection into gas chromatography/mass spec (GC/MS)
Agenda

- BioPhorum Operations Group
- The Disposables Workstream
- ISPE outline proposal
- BPOG value add and next steps
The work of the BPOG Disposables – Extractables Team

- The Extractables Team represents 15 of the member companies

- The team’s work
  - Confirm solvents and extractable conditions to cover 95% of requirements
  - Identify instrument conditions and analysis parameters to provide comparable results
  - Outline sample preparation standard and notification and refresh requirements
  - Socialize the proposal with the supply industry and gain feedback
  - Detail and hand off the technical content to a suitable standards agency

- Collaboration is progressing well
  - Wide consensus on the proposal with only minor modifications to date

- Statement of User Requirements in the next three months
  - Consultation with suppliers
  - Presentation at BPSA in July
QUESTIONS

Tony White
Director, BPOG
Open Discussion
Wrap-up;
Review Actions

Bob Steininger